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Interval Carcinomas of the Breast: A Group With Intermediate Outcome

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Background: Interval carcinoma is defined as a carcinoma detected between two mammographic screening rounds after a negative screening. By some authors these carcinomas are considered to be more aggressive than screen-detected carcinomas.
Methods: In a group of 937 patients referred for breast cancer in the period 1975–1990, 76 interval carcinoma patients were treated. In a retrospective study the outcome was studied of patients with an interval carcinoma in comparison with patients with screen-detected carcinomas and of patients with clinically detected carcinomas outside the screening program.
Results: No significant difference was found in the 5-year and 10-year disease-free survival of patients with interval carcinoma (80%, 68%) and the screen-detected group (89%, 81%) ($P = 0.12$). The interval group did significantly better than the patients with carcinomas detected outside the screening program ($P = 0.03$).
Conclusion: Interval-detected cancers for patients in the screening program had an outcome intermediate between patients with screen-detected cancers and patients with cancers detected outside the screening program. The difference between interval-detected cancers and cancers detected outside the screening program was significant, whereas the difference between screen-detected and interval cancers was not.

KEY WORDS: **interval carcinoma, breast neoplasms, screening, survival**

INTRODUCTION

With the introduction of breast screening programs by means of mammography a new entity called "interval breast cancer" has become a subject of study and controversy. These interval carcinomas, defined as carcinomas detected between two mammographic screening rounds after a negative screening, are suggested to be a more aggressive subset of breast neoplasias. Not all studies confirm the hypothesis of increased malignant behaviour [1,2], although in some studies at least a part of this group is more virulent, because of rapid growth and worse histopathological features [3–5].

To contribute to the discussion on the clinical behavior of interval carcinomas, we performed a retrospective analysis of interval carcinomas, comparing them with carcinomas detected by screening and carcinomas found without screening intervention.

MATERIALS AND METHODS

Patients

In Nijmegen, a population screening program for breast cancer disease started in January 1975. All women born before January 1, 1940, were invited to attend a bi-annual examination consisting of bilateral mammography. Only one view of each breast was made in the lateromedial projection. Physical examination was not included, but women were taught how to be alerted by symptoms and how to perform breast self-examinations. Initially the attendance rate for the first screening round was 75%

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(~20,000 women); in the age group 70 and over, this rate was <25% (~3,000 women). Stratification according to birth cohort showed little effect of screening in the youngest cohort age of 35–49 at entry, and in the group of women >70, only few attended screening; therefore, later on only women ages 50–70 were invited [6].

We reviewed the hospital records of all patients referred to our hospital for primary breast cancer in the period 1975–1990. The total of 937 breast cancer patients was divided into three separate groups: in these patients, 173 carcinomas were detected by screening mammography (group 1) and 76 patients presented with interval carcinomas (group 2); another 688 patients were treated without screening intervention (group 3). This last group consisted of patients who were never invited to attend the screening program, patients who chose not to attend, and patients who developed breast cancer >2 years after attending the screening program.

Patient age by detection varied from 35–89 years, with a mean age of 55 years. In age group 35–49, there were 319 patients (34%); 34 (11%) of these patients were detected by screening mammography, 253 patients (79%) were detected independent of the screening program, and 31 (10%) patients presented with an interval carcinoma. A total of 468 women (50%) presenting with breast cancer were aged 50–69%. Of these 14 (24%), were detected by screening, 314 (67%) were detected independent of screening, and 40 patients (9%) had an interval carcinoma. Only 151 (16%) of the patients were age 70 and over; 25 (17%) of whom were screen-detected, 121 (80%) detected independent of screening, and 5 (3%) detected in the interval between two screening rounds.

Treatment

The treatment modality has changed in the course of time. Before 1977, radical mastectomy was the usual treatment for lateral carcinomas, whereas centrally and medially situated tumours were treated by simple total mastectomy combined with postoperative irradiation of the regional lymph nodes (McWhirter). Since 1977 modified radical mastectomy has been the treatment of choice for both lateral and central-medial tumours.

To determine whether different modes of detection are associated with different survival rates, we determined the disease-free interval and breast cancer survival rates of all invasive tumours in each group. Carcinoma-in-situ (CIS) was left out in calculating disease-free survival and breast cancer survival rates, as CIS turned out to be a totally different group with good prognosis compared to invasive ductal and lobular types. Part but not all of the CIS will eventually become malignant, thus making comparison with already invasive (malignant) tumours invalid.

Furthermore, we determined features such as tumour size, histological type, and axillary lymph node status.

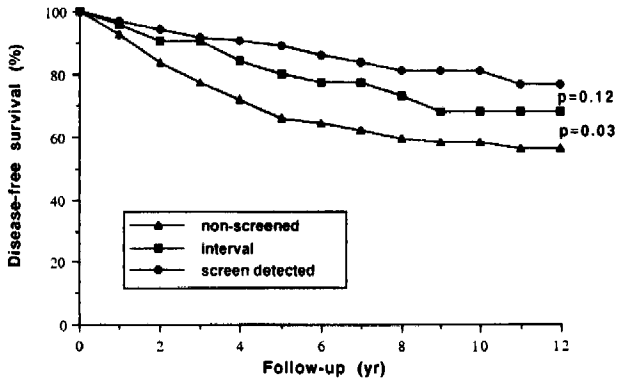

Fig. 1. Actuarial disease-free survival curves of the three groups of breast cancer patients.

Tumour size was assessed on the basis of the pathology report. Tumour size varied from 0.25–13.0 cm with a mean size of 2.5 cm.

Histologically, we classified all tumours into three types: carcinoma in situ, infiltrating ductal carcinoma with variants (including medullary, tubular and other special types) and, infiltrating lobular carcinoma. In 18 cases the exact histology could not be assessed.

Axillary nodal status was considered to be negative if no metastases were found in all lymph nodes examined, positive if lymph node metastases were found. The apical axillary node was always marked separately in axillary dissections. Metastases found in this node are referred to as positive top. In 135 patients axillary nodal status was not known, because in the first years of study no axillary dissections were done for the reason mentioned before.

Results were analysed for significance by a Log-Rank model with confidence limits at $P = 0.05$. Relative risk ratio's (RR) were obtained with the Chi proportional hazard regression model.

RESULTS

The 5-year and 10-year disease-free survival of the interval-detected group was 80% and 68%, of the screen-detected group 89% and 81%, and the control group 66% and 58%, respectively (Fig. 1). The difference between the interval group and the screen-detected group was statistically not significant ($P = 0.12$). The relative risk (RR) of recurrence of the disease initially found by screening compared to interval carcinomas is 0.6. The difference between the interval cancers and the cancers detected outside the screening program was found to be statistically significant ($P = 0.03$, RR = 1.7).

Comparable differences in all three groups were found when calculating breast cancer survival rates. The 5-year and 10-year breast cancer survival of the interval-detected group was 94% and 78%, of the screen-detected group 93% and 89%, and of the control group 81% and 65%, respectively. There was no statistical difference between

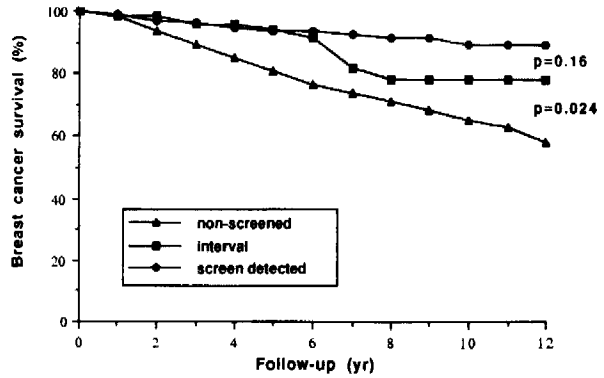

Fig. 2. Actuarial breast cancer survival curves of the three groups of breast cancer patients.

TABLE I. Carcinoma of the Breast: Distribution of Tumours According to Size

Tumour status	Screening	Interval	Other
T1 (≤2 cm)	114 (66%)	36 (48%)	296 (43%)
T2 (2–5 cm)	43 (25%)	32 (42%)	310 (45%)
T3 (>5 cm)	16 (9%)	8 (10%)	82 (12%)

TABLE II. Carcinoma of the Breast: Distribution of Axillary Lymph Node Status of the Three Groups*

	Screening	Interval	Other
Negative	100 (67%)	35 (50%)	255 (44%)
Positive	28 (19%)	29 (40%)	186 (32%)
Top node positive	22 (14%)	7 (10%)	138 (24%)

*In 137 cases, axillary lymph node status was unknown.

the interval-detected group and the screen-detected group ($P = 0.16$, RR = 0.5) in contrast to the difference between the interval-detected group and the control group ($P = 0.024$, RR = 2.1).

To see whether these results were consistent, some tumour features were determined and the possibility of intergroup differences in confounding variables was explored.

Table I shows the distribution of tumours according to size (T stage) for all three groups. A statistically significant difference was found in tumour size ($P = 0.0001$) with smaller tumours in the screen-detected group (66% T1 tumours). Only 48% of the interval carcinomas were categorized as for T1 tumours and 43% in the clinically detected carcinomas. But when adjusted for tumour size, RR ratios only change marginally and the statistically significant differences between the groups remain the same.

Only 33% of patients in the screened group showed axillary lymph node metastases, 14% had a positive top node. Of the interval cancers 50% presented with axillary metastases of which 10% with a positive top node. Of the nonscreened patients, 56% had axillary lymph node metastases and 24% of these had a positive top node (Table II). Of the patients in the screen-detected group, 13% had extra-nodal tumor growth, this being 26% for the interval-detected group and 36% in the nonscreened group ($P = 0.0001$).

TABLE III. Carcinoma of the Breast: Histology of the Three Different Groups*

	Screening	Interval	Other
In situ carcinoma	14 (8%)	1 (2%)	24 (4%)
Invasive ductal carcinoma	138 (90%)	58 (78%)	543 (80%)
Invasive lobular carcinoma	20 (12%)	15 (20%)	107 (16%)

*Histology was not known in 17 cases.

Also, histology showed some differences (Table III). In the screen-detected group we found DCIS in 8% of the patients, in the interval-detected group in 2%, and in the nonscreened group in 4%. The number of invasive lobular carcinomas was lowest in the screen-detected group (12%) with 16% in the nonscreened group and 20% in the interval-detected group ($P = 0.03$).

DISCUSSION

Screening of asymptomatic women for breast cancer is today a well-accepted procedure as secondary prevention of this potentially lethal malignancy. The so-called interval carcinoma is a new entity emerging from breast cancer screening programs and may in some cases be considered as a failure of screening. This screening error should be prevented particularly if interval carcinomas represent a category of malignancies with a worse prognosis in comparison with the screen-detected carcinomas.

We found that the interval carcinomas of the breast represent a group with intermediate outcome compared with tumours detected by screening and tumours found without screening intervention.

Comparing the survival rates of screen-detected cancers and interval cancers, the benefit of the first group is not significant, but data of disease-free survival and breast cancer survival indicate a tendency to better prognosis in the screen-detected group. Some studies indicate that there is a difference in outcome comparing the first screening round with successive rounds, making results in next rounds more favourable for the screen-detected group. In this study we did not take that into account.

Our results do not corroborate the results of DeGroote and coworkers [3], who found in a relatively small series a significantly higher incidence of axillary nodes and a lower 6-year survival for interval carcinomas.

Another finding is that the screen-detected group had a significantly more favourable outcome than the non-screen-detected group. The 5-year disease-free survival

of 89% of the screen-detected group is almost 25% better than that of patients with carcinomas detected outside the screening program (66%), and this benefit has lasted for at least 10 years. This figure corresponds well with that of other studies [7].

The screen-detected group appears to consist of smaller tumours with less axillary node metastases, so screen-detected cancers will have better prognosis as they represent a group with favourable stage (which was the first aim of breast cancer screening). Not only smaller tumour size and less axillary lymph node metastases cause this benefit, but also better histological features suggesting low malignant potential are present in the screened group as stated by Kallioniemi et al. [8].

When comparing interval cancers with cancers detected independent of screening, interval cancers show better results with significantly better disease-free survival and overall survival. Also, in other studies a similar trend toward higher survival rate of the interval group was found [1]. Looking for confounding variables, no clear intergroup differences could be found, interval breast carcinomas show only slightly better features (e.g., smaller tumour size and less axillary metastases) than the group of breast cancers detected independent of screening.

It is suggested that comparison with screen-detected cancers would be invalid since these carcinomas, because of length-bias sampling, constitute another subgroup of cancers with a certain proportion of slow-growing tumours, possibly including some that would not have become clinically manifest during the patient's lifetime [8,9]. In other studies a large proportion of DNA-aneuploid or otherwise malignant tumours were found in the interval group, also suggesting a more aggressive behaviour [10]. In a recent study by Arnerlöv and coworkers [11], the carcinomas detected during screening were characterized by small tumor size, a predominance of stage I cases, a tendency for DNA euploidy, long doubling time, and low S-phase fraction when compared with interval and clinically detected carcinoma. If according to these data only comparison to breast cancers found independent of screening is valid, our finding of interval carcinomas not being more aggressive remains. One explanation for this could be the fact that interval carcinomas represent a heterogeneous group consisting of "true" interval cancers (mostly rapidly growing malignant tumours), "unrecognized" tumor signs on previous mammography, and "observer errors" [10]. This group thus also contains de novo cancers that did not have the characteristics of rapidly growing tumours, pre-existing slowly proliferating tumours, and mammographically occult tumours. Rapidly growing highly malignant tumours are present in the interval group, but also a part of the carcinomas found without screening intervention will be rapidly growing. Thus the group of interval carcinomas seems not to be different from those in the nonscreened group.

Why the patients with interval cancers in our study had a more favourable outcome in comparison to the group found independent of screening can be partly explained by patient self-selection. Women who attend screening programs (women with interval carcinomas also did) are likely to be more alarmed by small symptoms than women who postpone medical examination (or not attend screening) despite the presence of alarming symptoms [11].

The occurrence of an interval carcinoma of the breast always will be a disappointment, not only to women themselves, but also to health personel conducting screening programs. But data in our study show that even interval cancers have a better prognosis than the group of breast cancers detected without screening intervention.

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REFERENCES

1. Holmberg LH, Adami HO, Tabár L, Bergström R: Survival in breast cancer diagnosed between mammographic screening examinations. Lancet II:27–30, 1986.
2. Frisell J, Eklund G, Hellström L, Somell A: Analysis of interval breast carcinomas in a randomized screening trial in Stockholm. Breast Cancer Res Treat 9:219–225, 1987.
3. DeGrootte R, Rush BF, Milazzo J, et al.: Interval breast cancer: A more aggressive subset of breast neoplasias. Surgery 94:543–547, 1983.
4. Anderson I. What can we learn from interval carcinomas? Recent Cancer Res 90:219–225, 1984.
5. Ikeda DM, Andersson I, Wattsgård C, et al.: Interval carcinomas in the Malmö mammographic screening trial. Radiographic appearance and prognostic considerations. Am J Roengenol 159:287–294, 1992.
6. Hendriks JHCL. Population screening for breast cancer by means of mammography in Nijmegen, 1975–1980, thesis, Nijmegen University, Nijmegen, Thieme bv, 1982.
7. Crisp WJ, Higgs MJ, Cowan WK, et al.: Screening for breast cancer detects tumours at an earlier biological stage. Br J Surg 80:863–865, 1993.
8. Kallioniemi O, Kärkkäinen A, Auvinen O, et al.: DNA flow cytometric analysis indicates that many breast cancers detected in the first round of mammographic screening have a low malignant potential. Int J Cancer 42:697–702, 1988.
9. Klemi PJ, Joensuu H, Toikkanen S, et al.: Aggressiveness of breast cancers found with and without screening. Br Med J 304:467–469, 1992.
10. Rosen von A, Erhardt K, Hellström L, et al.: Assessment of malignancy potential in so-called interval mammary carcinomas. Breast Cancer Res Treat 6:221–227, 1985.
11. Arnerlöv C, Emdin SO, Lundgren B, et al.: Breast carcinoma growth rate described by mammographic doubling time and S-phase fraction. Cancer 70:1928–1934, 1992.